Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

silthiofam (ISO); *N*-allyl-4,5-dimethyl-2-(trimethylsilyl)thiophene-3-carboxamide

EC Number: -
CAS Number: 175217-20-6

CLH-O-0000001412-86-245/F

Adopted

30 November 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILTHIOFAM (ISO); *N*-ALLYL-4,5-DIMETHYL-2-(TRIMETHYLSILYL)THIOPHENE-3-CARBOXAMIDE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: silthiofam (ISO); *N*-allyl-4,5-dimethyl-2-(trimethylsilyl)thiophene-3-carboxamide
EC number: -
CAS number: 175217-20-6
Dossier submitter: Ireland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2018	Germany		MemberState	1
Comment received				
The DE-CA supports the proposed classification. However the precautionary statements P391 and P501 should be cancelled in the dossier, because precautionary statements are not part of Annex VI part 3 of the CLP Regulation. In addition EUH401 should be cancelled. According to Annex II Part 4 of the CLP Regulation EUH401 is exclusively intended for PPP active substances where it is a complementary labelling statement according to Annex II Part 4 of the CLP Regulation and no supplementary hazard statement according to Annex II Part 1 of the CLP Regulation.				
Dossier Submitter's Response				
Thank you for your support. Precautionary statements can be removed.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2018	Belgium		MemberState	2
Comment received				
BE CA thank the IR CA for this CLH proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silthiofam.docx				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILTHIOFAM (ISO); *N*-ALLYL-4,5-DIMETHYL-2-(TRIMETHYLSILYL)THIOPHENE-3-CARBOXAMIDE

Dossier Submitter's Response
Thank you for your comments. Please see response at 14 below.
RAC's response
Thank you for your comments. Please see response at 14 below.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	3
Comment received				
Due to the size of the files, several submission are made. This is the continuity of submission 56016c36-8b69-4f3b-a586-1676a52a3875, 5e0a94fd-10d5-4ad3-8c8a-c1d4888abcdf, 2b5eb86b-fa06-4612-91bb-12eacb363962 and c80c158c-1f58-48ce-88c5-d2cbab2b73fd, 8ed23501-0414-443b-818b-3f210dd9ae7a ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 6 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip			
Dossier Submitter's Response				
Noted. Please see response at 21 below.				
RAC's response				
Noted. Please see response at 21 below.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	4
Comment received				
Due to the size of the files, several submission are made. This is the continutity of submission 56016c36-8b69-4f3b-a586-1676a52a3875, 5e0a94fd-10d5-4ad3-8c8a-c1d4888abcdf, 2b5eb86b-fa06-4612-91bb-12eacb363962 and c80c158c-1f58-48ce-88c5-d2cbab2b73fd ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 5 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	5
Comment received				
Due to the size of the files, several submission are made. This is the continutity of submission 56016c36-8b69-4f3b-a586-1676a52a3875,				

5e0a94fd-10d5-4ad3-8c8a-c1d4888abcdf and 2b5eb86b-fa06-4612-91bb-12eacb363962 ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 4 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	6
Comment received				
Due to the size of the files, several submission are made. This the continutity of submission 56016c36-8b69-4f3b-a586-1676a52a3875 and 5e0a94fd-10d5-4ad3-8c8a-c1d4888abcdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 3 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	7
Comment received				
Due to the size of the files, several submission are made. This the continuity of submission 56016c36-8b69-4f3b-a586-1676a52a3875 ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 2 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	8
Comment received				
The submission consisted of 6 files. Due to size limitations, the files will be submitted with the diffrent submissions				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 1 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip
Dossier Submitter's Response
Noted
RAC's response
Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2018	Belgium		MemberState	9
Comment received				
Tumours have been shown in two different species after silthiofam exposure. First, a statistically significant increase in the incidence of hepatocellular adenomas in high-dose females has been reported at 4000 ppm in a mouse 18-month dietary carcinogenicity study. These tumours have been considered secondary to sithiofam-induced liver toxicity. Observations of hepatotoxicity included increased ALT and AST and individual cell necrosis. Histopathological reporting at same dose also included hepatocellular hypertrophy, cystic degeneration, karyomegaly, mixed cell foci, pigment deposition in Kuppfer cells and cytoplasmic vacuolation. In a rat 2-year dietary carcinogenicity study, increases in hepatocellular tumours and in thyroid follicular tumours in high-dose males have been reported at 3000 ppm, associated with increased gamma GT, hepatocellular hypertrophy, vacuolation, eosinophilic foci and cystic degeneration. The DS concluded that carcinogenicity findings might be considered as treatment-related in mouse and rat. However, they argued that the observed tumours in rat and mouse should be considered not relevant to human because the MoA is supposed to be CAR/PXR mediated. The conclusion on the postulated MoA mainly relies on CYP2B1, CYP2B2 and CYP3A1 activation and liver hypertrophy/cell proliferation after silthiofam exposure. BE CA aknowledge that some evidences suggest a CAR/PXR mediated MoA. However, we consider that the evidences are not sufficient to conclude that this mode of action is established as the origin of the observed tumours and that the human relevance is excluded. In particular, BE CA is of the opinion that the other potential mode of actions have not be sufficiently excluded because some findings indicate that hepatotoxicity might be involved in the appearance of tumours after sithiofam exposure. Indeed, in vitro testing showed that cytotoxicity, as demonstrated by the decrease in ATP release, indicating cytotoxicity, only occured at high doses whereas the activation of CYP2B1, CYP2B2 and CYP3A1 occurred from lower doses. At the opposite, no dose-dependant increase in tumours is observed after sitlhiofam exposure, the neoplastic observations in carcinogenicity studies only occurring at top dose in both species. Moreover, the tumour formation was associated with necrosis and increased ALT/AST in the 18-month mouse dietary carcinogenicity study, suggesting that cytotoxicity might be the potential mode of action. BE CA also note that CYP1A activation, a marker of AhR, was not evaluated. As a general conclusion, BE CA is of the opinion that the mode of action leading to rat and mouse neoplastic findings remains unclarified and that the relevance to human cannot be				

excluded. Therefore, on the basis of the CLH report, we support a Carc. 2 classification.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silthiofam.docx

Dossier Submitter's Response

The DS welcomes the comments from BE and has an understanding for their position.

The tumours of concern are:

(1) Female mouse: 18 month dietary study; increased incidence of liver adenomas at the highest dose (855 mg/kg bw/day; 5/50 animals, 10%) above concurrent controls (1/50 animals, 2%) and historical control data (max 3/8%, contracted testing lab/Charles River laboratories)

(2) Male rat: 2 yr dietary study; increased incidence of liver adenomas at the highest dose (150 mg/kg bw/day; 7/50 animals, 14%) above concurrent controls (4/50 animals, 8%) and historical control data (0-8%)

(3) Male rat: 2 yr dietary study; increased incidence of liver carcinomas at the highest dose (150 mg/kg bw/day; 4/50 animals, 8%) above concurrent controls (0/50 animals, 0%) and historical control data (0-6.7%)

(4) Male rat: 2 yr dietary study; male rats show evidence of an increased incidence in thyroid follicular adenomas at the highest dose (150 mg/kg bw/day; 5/50 animals, 10%) above the concurrent controls (3/50 animals, 6%) but not the HCD (1.7 – 12%).

(5) Male rat: 2 yr dietary study; male rats show evidence of an increased incidence in thyroid follicular carcinomas at the highest dose (150 mg/kg bw/day; 2/50 animals, 4%) above the concurrent controls (0/50 animals, 0%) but not the HCD (1-4%).

The DS notes mechanistic evidence to suggest a CAR/PXR mediated MoA:

(1) 14 day in-vivo rat study:
- Substantial induction of hepatic CYP2B1, CYP2B2 and (to a lesser extent) CYP3A1 (based on enzyme activity, mRNA expression and Western blot data).
- substantial increase in replicative DNA synthesis (cell proliferation) was also observed in the livers at 7 and 14 days.
- No evidence of activation of PPARα (as measured by enzyme activity, gene expression and Western blots).
- Increased induction of hepatic T4-UDPGT activity was observed after 14 days of dosing.

(2) Rat wild-type hepatocyte in-vitro study (phenobarbital and silthiofam tested):
- Silthiofam acted in a phenobarbital manner
- Increased induction of CYP2B1, CYP2B2 and CYP3A1 (revealed by enzyme activity, mRNA expression)
- Increase in replicative DNA synthesis (cell proliferation), EGF positive control was satisfactory.
- Cytotoxicity at silthiofam concentrations > 100µM

(3) Human hepatocyte in-vitro studies (comparison of phenobarbital and silthiofam):
- Silthiofam acted in a phenobarbital manner
- No increase in PROD activity (CYP2 marker), weak response in BROD and BQ activity (CYP2/ CYP3 and selective CYP3 markers respectively)
- Weak induction of CYP2 and CYP3 mRNA expression
- **NO** increase in replicative DNA synthesis (cell proliferation), EGF positive control was satisfactory.
- Cytotoxicity at silthiofam concentrations > 100µM

(4) Rat CARKO/PXRKO hepatocyte in-vitro study (phenobarbital and silthiofam tested):
- No increase in PROD, BROD or BQ enzyme activity relative to controls.
- Weak effect on CYP2B1 but no effect in CYP2B2 or CYP3A gene expression.
- **No** increase in cell proliferation, EGF positive control was satisfactory.
- Cytotoxicity at silthiofam concentrations > 100µM

Other modes of action were not investigated and there were no in-vivo studies with CAR/PXR knock out animals. The DS is of the opinion that the data from silthiofam treatment is supportive of a CAR/PXR mediated effect on rodent liver and does not propose classification for carcinogenicity.

RAC's response

With regard to rat liver tumours, in the carcinogenicity study, liver tumours were observed in absence of significant liver toxicity such as necrosis, fibrosis or inflammation. In the 90-day rat repeated-dose toxicity study, liver toxicity was observed but necrosis was not found. RAC agrees with the DS that based on the evidence a CAR/PXR mediated MoA not relevant to humans is plausible for the rat liver tumours. Nevertheless, uncertainties have been noted by RAC. Indeed, no *in vitro* studies on female rats have been performed to investigate differences in sexes observed in the carcinogenicity study. Moreover, some MoA were not excluded (e.g. AhR activation). With regard to thyroid tumours, as the tumours were not statistically significant and not above historical control data of this strain of rat, these tumours are considered to be of less concern.

Nevertheless, with regard to mouse liver tumours, RAC agrees that tumours occurred in presence of cytotoxicity as necrosis was observed in both sexes. Nevertheless, higher toxicity was observed in males than in females and no increase in liver tumours were observed in males, as also this may have been expected. As silthiofam was not genotoxic and as tumours in females did no progress to malignancy, RAC agrees with the DS's proposal for no classification.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Denmark		MemberState	10
Comment received				
Not assessed.				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Denmark		MemberState	11
Comment received				
It is noted that there is no mentioning of sufficient target tissue exposure in the in vivo micronucleus study in mouse neither in the RAR nor in the CLH report. If there is no data showing sufficient exposure of the bone marrow, the negative result of the study should not be considered.				
Dossier Submitter's Response				
ADME studies indicate that absorption was calculated to be 91.6% for the single low oral dose males, 99.6% for the single high oral dose males and 87.0% for the repeated oral dose in males. There is no reason to believe that the target tissue was not exposed. Bioaccumulation potential is low due to rapid excretion with the urinary system being the major route of elimination (up to 60%). Elimination of the dose was rapid with 87.3-93.7 percent of the dose excreted within 48 hours after dosing. Examination of the tissue distribution of radioactivity by whole body autoradiography at 8 hours after dosing indicated that radioactivity was widely distributed amongst all organ systems.				
RAC's response				
RAC agrees that as no proof of exposure was available in the *in vivo* micronucleus assay, the negative results cannot be used to conclude that the substance is not genotoxic. Neverthless, based on the negative *in vitro* studies and *in vivo* UDS, no classification is warranted for silthiofam.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2018	Netherlands		MemberState	12
Comment received				
The NL CA tends to agree with the classification as Repr. 2; H361d for silthiofam, based on an increase in the number of dead fetuses and an increased incidence of cleft palate observed in a rat developmental study (OECD 414) at the 1000 mg/kg bw/day dose level. Cat. 2 seems appropriate, considering the effects are severe but only occurred at a high dose level that also induced considerable maternal toxicity, the effects were not observed in other studies, and the effects each occurred in only two litters. Maternal toxicity cannot be excluded as a cause for the other observed effects (i.e. reduced fetal weight, reduced ossification and an increase in the occurrence of the 7th cervical rib). Both fetal mortality and cleft palate were observed in the rat developmental study in two litters. As there was significant maternal toxicity at this dose level, we would like to ask whether there is individual data available that may be used to ascertain whether these dams were particularly affected. Furthermore, when the litter with multiple malformed pups is excluded, the occurrence of cleft palate falls within the historical control range (0.3% per litter). It would be especially relevant to know the occurrence of cluster litters with cleft palate within the historical control data. This will provide more insight into whether the second litter with multiple malformed pups can be considered treatment-related or not.				

Dossier Submitter's Response
Thank you for your comment. There are two main questions; **firstly**, can marked maternal toxicity be sometimes associated with a specific malformation in addition to general developmental retardation The notifier has provided (in the public consultation) a detailed analysis of the relative maternal toxicity in the 2 dams which bore the litters with cleft palates (Doc 20180622). In addition, a detailed analysis of the individual foetuses was submitted. The data clearly support the conclusion that the high dose (1000 mg/kg bw/day) was greater than the maximum tolerated dose and that significant maternal toxicity was demonstrated. In addition, the dams of the affected litters were particularily affected. The litters in question also demonstrated clear toxicity (reduced weight/ossification) in addition to cleft palate. The argument was made that in individual dams with particular maternal toxicity, decreased foetal weight/retardation can be associated with an increased incidence of cleft palate. A number of published papers were provided ((Shah and Travill, 1976; Shah, 1979; Khera, 1985; Khera, 1987; Katz, 1988; DeSesso and Scialli, 2018). However, we note that many substances causing significant marked maternal toxicity do not necessarily cause cleft palate by a non-specific mechanism. **Secondly,** how to deal with the cluster of cleft palates in a single litter. The point is made in the CLH report that a cluster of malformations should be considered in a different way to an increased number of individual foetuses with malformations in separate litters. There is no historical data available to the DS on the occurrence of clusters of cleft palate.The question to the experts is whether a cluster of a single rare malformation should be treated in the same way as a litter with multiple malformed foetuses or as a single litter incidence of that malformation. Also, how do we regard the occurrence of the same malformation in another litter of that same treatment group. The litter is the appropriate experimental unit in developmental toxicity studies and so strictly speaking, this study had 2 litter instances which is outside the HC supplied. In our opinion, the adverse foetal findings at the high dose are clearly associated with marked foetal toxicity which is most likely to be (at least partly) linked to marked maternal toxicity. Only the rat is affected and no adverse effects were seen at the mid dose of 500 mg/kg bw/day; also a very high dose. In a very strict sense, classification is probably warrented because of the severity of the foetal effects and certainly should be thoroughly discussed, however a strong argument can be made for non classification.
RAC's response
Thank you for your comment and response. RAC agrees that cleft palate, dead foetuses and skeletal variations occurring in several litters are severe enough to warrant classification. Nevetheless, as marked maternal toxicity was observed in dams having malformed foetuses, no classification has been adopted by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2018	Italy	Federchimica	Industry or trade association	13
Comment received				
Silthiofam should not be considered as toxic to embryo- foetal development and the proposed classification as Repro. 2. (H361d) is not justified. The effects on development reported above in the rat occurred in the presence of significant maternal toxicity. It is clear that the dose level of 1,000 mg/kg bw/day is greater than the maximum tolerated dose (MTD) and should be excluded from the embryo- foetal developmental evaluation of Silthiofam. The maternal body weight gain of the 1,000 mg/kg bw/day group was statistically significantly ($p<0.01$) decreased when				

compared to the respective control values. For dam 43188, of which the litter exhibited a high incidence of cleft palate, daily food consumption, the net body weight and net body weight gain were decreased by 23%, 13%, and 66% when compared to the respective group mean control values. There were substantial clinical signs of maternal toxicity and combined with the effects on food consumption, net body weight and net body weight gain, it is considered that these effects of maternal toxicity have produced a substantial retardation in foetal development resulting in an increased incidence of cleft palate. The association between cleft palate and retardation in foetal development has been documented in the literature.

The increased incidence in cleft palate is limited to a single litter is a secondary effect of the maternal toxicity observed at the high dose of 1,000 mg/kg bw/day and therefore, Silthiofam should not be considered as a compound having a selective effect on morphogenesis. The numerical increase of dead foetuses was small, not statistically significant and can be considered to be of limited relevance for the evaluation of embryo- foetal development because there was no concurrent decrease in viable foetuses or an increase in post- implantation loss when compared to the controls. Additionally, the 2 litters in which dead foetuses were recorded, showed significantly decreased mean foetal body weights with substantial clinical signs of toxicity in the respective dams.

Based upon the severity of the maternal toxicity observed at the high dose and the evidence available in the literature that associates maternal toxicity with developmental retardation, which under certain circumstances can manifest itself as cleft palate, Silthiofam should not be considered as toxic to embryo- foetal development and the classification as Repro. 2. (H361d) is not warranted.

Dossier Submitter's Response

Thank you for your comments. The proposal for classification as Repro. 2. (H361d) was made on the basis of the observed serious and rare malformations in the rat main study in conjunction with pup deaths and increased incidence of 7th cervical rib. Attention was drawn to the degree of maternal toxicity at the effects dose level. Additional detailed analysis of the maternal and foetal toxicity data has been submitted and will no doubt be considered in the RAC discussions.

RAC's response

Thank you for your comment and response. Reproductive toxicity observed in the rat developmental toxicity study has been considered severe but occurred in the presence of severe maternal toxicity. Thus no classification was agreed by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2018	Belgium		MemberState	14

Comment received

For the correct display of the added table see the uploaded document.

Fertility

In Table 54 (p.98 of CLH report), the n° of pregnant dams, fertility index and number of pups are the following :
Gen 0 ppm 40 ppm 400 ppm 4000 ppm
Females on study F0
F1 30
30 29
30 30

30 29
30
N° of pregnant dams F0
F1A 67
63 83
77 83
67 97
83
Fertility index % F0
F1A 69
63 89
79 93
71 97
83
N° of pups (total) F0
F1A 274(20)
250(19) 365(24)
302(23) 370(25)
252(20) 384(28)
332(24)

The results for the control are lower than 70% whereas the results for the top dose do not seem to be coherent with the reported maternal toxicity (decrease in mean body weight and hepatotoxicity). We would appreciate some clarifications regarding these results. Either the control should be considered invalid due to the low fertility index or there is an error in the reporting.

Considering that this study is the only available study to assess the toxicity on fertility of silthiofam, BE CA is of the opinion that this question should not remain unresolved.

Developmental toxicity

Rat developmental toxicity (WIL-50240) : maternal toxicity at top dose, associated with dead fetuses an decreased fetuse weight. Reporting of external malformations (umbilical herniation and cleft palate) and skeletal variations (unossified sternebrae/cervical centrum)

A rabbit developmental toxicity study (WI-96-105) is also available in the CLH report. The dose levels have been adequately chosen based on a previous dose-range findings developmental toxicity study. No treatment-related clinical findings are reported in dams but a number of external, soft tissues and skeletal malformations were identified in the fetuses.

Unfortunately, no detail is provided about the specific type of malformations. Therefore, considering that the malformations occurred in absence of maternal toxicity, BE CA is of the opinion that this study might be considered as one of the key studies for the classification of silthiofam as a reproductive toxicant. Therefore, we are of the opinion that no conclusion can be drawn without further clarifications regarding the specific skeletal, external and soft tissues variations and malformations reported for each dose-group.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silthiofam.docx

Dossier Submitter's Response

Fertility study (Lemon 1997): With regard to the Table 54 (p 98 of the CLH report): The data presented for the number of pregnant dams is correct but would be better/more clearly described as the number pregnant/total paired (%). The fertility index of the controls (< 70%) is lower than the treated groups at all dose levels and the difference is statistically significant at the high dose level.
Test house HC data (N = 5): mean 84.66 range 80 – 93.3)
Charles River HC (Horsham PA; 2008-2016) 189 studies: min 76%, maximum 100%.
However, there is no effects on fertility parameters in the treated groups so while the control group fertility appears to be significantly lower than the other groups, this does not in our view warrant negation of the study.
The data on maternal body weight/weight change (Table 51 and 52) and pathology (Table 53) are reported correctly. They show clear effects on maternal body weight and weight gains and also that the liver is a target organ at the highest dose level of 4000 ppm.
It is therefore concluded that even though maternal toxicity is clearly demonstrated at the high dose, fertility was not affected.

Developmental toxicity:
Rat study (WIL-50240): All data necessary for hazard assessment are presented.
Rabbit study ((WI-96-105): A number of external, soft tissues and skeletal malformations were identified in the foetuses/litters but with no treatment or dose-relationship apparent. The individual findings were not tabulated for this reason. The tabulated data are attached to this file (attachment 1)
The RMS does not consider this study as relevant to classification for developmental toxicity.

RAC's response

Thank you for your comment and response. With regard to the fertility study, RAC agrees that control of the 2-generation rat study may not be appropriate. Nevertheless, there is no indication in the dossier that classification of silthiofam for fertility would be warranted.

With regard to developmental toxicity, RAC agrees with the DS that no findings in the rabbit developmental toxicity would warrant classification.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Denmark		MemberState	15

Comment received

The proposal for classification as Repr 2 (H361d) is supported based on findings in the rat developmental study (WIL 50240): Observations of dead fetuses (four dead fetuses from two litters; outside HCD) and cleft palate (nine fetuses from two litters, 8 in one litter; outside HCD) was seen only in the high dose group (1000 mg/kg bw/day) and possibly increased occurrence of 7th cervical rib observed in the highest dose group. Even though these findings were seen in the presence of maternal toxicity, malformations and fetal death should not generally be considered secondary to maternal toxicity.

Furthermore, classification for effects on or via lactation may be considered.
An effect on lactation may be possible based on results of the 2-generation study (MSL-15554), in which the mean pup weight in the highest dose was similar to controls at birth but from day 4 onwards was significantly reduced compared with controls; this was seen in both generations. A reduction already at LD4 and LD7 cannot be due to direct exposure

of pups via chow containing the test material. Furthermore, a reduced maternal bw loss during lactation in high dose dams was suggested in the RAR to be due to diversion of nutrients from milk to maintain maternal body mass:
'Mean pup weights were similar at birth, but were significantly lower than controls ($p<0.01$, $p<0.05$) from PN day 4 to PN day 21 at the high dose level. This observation was associated with maternal toxicity at this dose. The (statistically) significant lesser body weight losses in dams of this group from days 14 to 21 of lactation when compared to controls possibly indicates a diversion of nutrients from lactation to maintenance of body mass and thus causing poor thriving of pups. This group had significantly lower mean body weight (but not body weight gain) throughout gestation (Tables B6.6-1a/b).'
Furthermore, with a log POW of 3.72 for silthiofam and ADME data showing a wide distribution with fat, transfer of silthiofam or its metabolites via milk may be possible. There are no studies on residues in milk.

Dossier Submitter's Response

In principle we agree that classification may be warrented as malformations and foetal death should not generally be considered as secondary to maternal toxicity. However, we believe that an indepth analysis of the maternal and foetal toxicity data should be carried out in this case (as was submitted by the Industry) to ensure that the correct decision is made.
Lactation
Mean body weight of dams was slightly but significantly reduced (≤ 10%) at the high dose group throughtout gestation and lactation except for day 21 of lactation when it was not different from controls. Meanwhile, mean body weight change/loss was not significantly different except at the L14-21 day interval when it was significantly less than the controls and other treated groups. It appears that the dams held their body weight in this period where nursing dams generally lose weight overall. High dose level pups gained moderately (significantly) less weight during lactation than other groups. This may represent a more specific toxicity due to the test substance affecting either milk quality/quantity or a combination of maternal toxicity and systemic toxicity from ingesting treated diet later in lactation.
There are two main general criteria according to the guidance for classification;

1. a substance which negatively impacts milk quantity or quality in the absence of apparent maternal toxicity should classify for effects on or *via* lactation. In addition…"The type or magnitude of maternal effects and their potential influence on lactation/milk quality need to be assessed on a case-by-case basis to determine whether classification for effects on or *via* lactation is necessary"...
2. If the substance can enter the milk in sufficient quantities to cause direct toxicity to the offspring then maternal toxicity is not/less relevant.

We agree that classification for lactation should be discussed.

RAC's response

Thank you for your comment and response. Reprodcutive toxicity observed in the rat developmental toxicity study has been considered by RAC in regard to individual data and maternal toxicity. No data were available on the concentration of silthiofam and its metabolites in the milk. ADME data showed a wide distribution of silthiofam including into fat suggesting that transfer to milk may be possible. Nevertheless, the reduced mean pup weight may also coincide with the beginning of ingestion of the chow containing the test material. Therefore, no classification was proposed by RAC.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILTHIOFAM (ISO); *N*-ALLYL-4,5-DIMETHYL-2-(TRIMETHYLSILYL)THIOPHENE-3-CARBOXAMIDE

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	16
Comment received				
Certis Europe BV proposed some comments related to the Reproductive toxicity for the following paragraphs in the CLH report: • Paragraph 1.2 (page 7 table 2) , paragraph 1.3 (page 9 table 3 and page 10), Paragraph 2.2 (page 11), paragraph 4.11.2.1 (page 104), paragraph 4.11.4 (page 107), paragraph 4.11.5 (page 108), paragraph 4.11.6 (page 109) Reproductive toxicity : no classification and no labelling . Reasons : Adverse effects on development were observed at the 1000 mg/kg bw/day dose level which was clearly toxic to the maternal animal and above the MTD. The consequence of this maternal toxicity manifests as general growth retardation (reduced ossification, reduced foetal weights and increase in incidence of skeletal anomaly - 7th cervical rib) as well as occurrence of dead foetuses. The cleft palate should be considered to be a secondary, non-specific consequence of the maternal toxicity seen at the high dose level of 1000 mg/kg bw/day. Therefore, Silthiofam should not be classified for developmental toxicity ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 6 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip				
Dossier Submitter's Response				
Noted. Please refer to response to comment 21				
RAC's response				
Noted. Please refer to response to comment 21.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	17
Comment received				
Certis Europe BV proposed some comments related to the Reproductive toxicity for the following paragraphs in the CLH report: • Paragraph 1.2 (page 7 table 2) , paragraph 1.3 (page 9 table 3 and page 10), Paragraph 2.2 (page 11), paragraph 4.11.2.1 (page 104), paragraph 4.11.4 (page 107), paragraph 4.11.5 (page 108), paragraph 4.11.6 (page 109) Reproductive toxicity : no classification and no labelling . Reasons : Adverse effects on development were observed at the 1000 mg/kg bw/day dose level which was clearly toxic to the maternal animal and above the MTD. The consequence of this maternal toxicity manifests as general growth retardation (reduced ossification, reduced foetal weights and increase in incidence of skeletal anomaly - 7th cervical rib) as well as occurrence of dead foetuses. The cleft palate should be considered to be a secondary, non-specific consequence of the maternal toxicity seen at the high dose level of 1000 mg/kg bw/day. Therefore, Silthiofam should not be classified for developmental toxicity				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 5 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip
Dossier Submitter's Response
Please refer to response to comment 21
RAC's response
Noted. Please refer to response to comment 21.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	18
Comment received				
Certis Europe BV proposed some comments related to the Reproductive toxicity for the following paragraphs in the CLH report: • Paragraph 1.2 (page 7 table 2) , paragraph 1.3 (page 9 table 3 and page 10), Paragraph 2.2 (page 11), paragraph 4.11.2.1 (page 104), paragraph 4.11.4 (page 107), paragraph 4.11.5 (page 108), paragraph 4.11.6 (page 109) Reproductive toxicity : no classification and no labelling . Reasons : Adverse effects on development were observed at the 1000 mg/kg bw/day dose level which was clearly toxic to the maternal animal and above the MTD. The consequence of this maternal toxicity manifests as general growth retardation (reduced ossification, reduced foetal weights and increase in incidence of skeletal anomaly - 7th cervical rib) as well as occurrence of dead foetuses. The cleft palate should be considered to be a secondary, non-specific consequence of the maternal toxicity seen at the high dose level of 1000 mg/kg bw/day. Therefore, Silthiofam should not be classified for developmental toxicity ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 4 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip				
Dossier Submitter's Response				
Please refer to response to comment 21				
RAC's response				
Noted. Please refer to response to comment 21.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	19
Comment received				
Certis Europe BV proposed some comments related to the Reproductive toxicity for the following paragraphs in the CLH report: • Paragraph 1.2 (page 7 table 2) , paragraph 1.3 (page 9 table 3 and page 10), Paragraph 2.2 (page 11), paragraph 4.11.2.1 (page 104), paragraph 4.11.4 (page 107), paragraph 4.11.5 (page 108), paragraph 4.11.6 (page 109) Reproductive toxicity : no classification and no labelling . Reasons : Adverse effects on development were observed at the 1000 mg/kg bw/day dose level which was clearly toxic to the maternal animal and above the MTD. The				

consequence of this maternal toxicity manifests as general growth retardation (reduced ossification, reduced foetal weights and increase in incidence of skeletal anomaly - 7th cervical rib) as well as occurrence of dead foetuses. The cleft palate should be considered to be a secondary, non-specific consequence of the maternal toxicity seen at the high dose level of 1000 mg/kg bw/day. Therefore, Silthiofam should not be classified for developmental toxicity   ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 3 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip
Dossier Submitter's Response
Please refer to response to comment 21
RAC's response
Noted. Please refer to response to comment 21.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	20
Comment received				
Adverse effects on development were observed at the 1000 mg/kg bw/day dose level which was clearly toxic to the maternal animal and above the MTD. The consequence of this maternal toxicity manifests as general growth retardation (reduced ossification, reduced foetal weights and increase in incidence of skeletal anomaly - 7th cervical rib) as well as occurrence of dead foetuses. The cleft palate should be considered to be a secondary, non-specific consequence of the maternal toxicity seen at the high dose level of 1000 mg/kg bw/day. Therefore, Silthiofam should not be classified for developmental toxicity ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 2 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip				
Dossier Submitter's Response				
Please refer to response to comment 21				
RAC's response				
Noted. Please refer to response to comment 21.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	21
Comment received				
Adverse effects on development were observed at the 1000 mg/kg bw/day dose level which was clearly toxic to the maternal animal and above the MTD. The consequence of this maternal toxicity manifests as general growth retardation (reduced ossification, reduced foetal weights and increase in incidence of skeletal anomaly - 7th cervical rib) as well as occurrence of dead foetuses. The cleft palate should be considered to be a				

secondary, non-specific consequence of the maternal toxicity seen at the high dose level of 1000 mg/kg bw/day. Therefore, Silthiofam should not be classified for developmental toxicity ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 file 1 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip
Dossier Submitter's Response
The proposal for classification as Repro. 2. (H361d) was made on the basis of the observed serious and rare malformations in the rat main study in conjunction with pup deaths and increased incidence of 7th cervical rib. Attention was drawn to the degree of maternal toxicity at the effects dose level. The Industries' analysis of relative maternal and foetal toxicity is considered relevant and important to the discussion of the classification proposal for Repr 2 (H361d). The publications submitted are generally of marginal relevance to the specific issue of interpreting data generated in pregnant rats with silthiofam and the application of the classification criteria of the CLP Regulation.
RAC's response
The proposal for classification as Repr. 2; H361d has been considered by RAC. RAC agrees with the DS that the Industries' analysis of relative maternal and foetal toxicity was relevant and important to the discussion of the classification proposal for Repr. 2; H361d and that the publications submitted are generally of marginal relevance to the specific issue of interpreting data generated from pregnant rats following exposure to silthiofam. Overall, no classification was proposed by RAC in view of the high maternal toxicity observed in the dams.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2018	Belgium		MemberState	22
Comment received				
BE CA aknowledge that the liver is the target-organ, warranting a STOT RE 2 classification. However, we consider that the general observed mortality should be considered for a classification for STOT RE 2 (lethality) based on observed effects in dog and maybe also in rabbit. Indeed, mortality has been observed in at least four different species. In dog, the mortality is observed at doses warranting a classification when considering the time of death : In a 28-day repeated oral exposure in dog (MSL-14758, 0-10-50-150-350 mg/kg ; 2/sex/group), 2 males and 1 female were sacrified in extremis in the top-dose group. The dose was therefore reduced from 350 to 250 after 2 weeks (males) or 3 weeks (females). This observation indicates that the deaths occurred only after two or three weeks, increasing the concern for a STOT RE 2 classification. In a 90-day repeated oral toxicity study in dog (MSL-15197, 0-1-10-50 and 125 mg/kg bw/day; 5/sex/group), 1 female was sacrified on day 50 in the top-dose group. High dose was again reduced from 125 to 75 mg/kg after 7 weeks of study in females only. Some uncertainties also remain regarding the rabbit repeated dose toxicity study				

presented in the CLH proposal (WI-96-105). The dossier indicates that mortality occurred in rabbit at doses > 100 mg/kg. However, no detail is provided about the study, including duration and number of exposed rabbit, detailed clinical signs, number of deceased animals and time of death.

Moreover, in the rabbit dose-range findings developmental toxicity study (WI-95-239), massive deaths were reported at top dose (4/6 and 5/6 dead dams at 100 mg/kg and 150 mg/kg bw/day respectively). The deaths occurred after a short delay, on gestations days 13-16 after 100 mg/kg bw/day exposure and after gestations days 15-22 after 150 mg/kg bw/day.

A statistically significant reduction in survival in females at 10 and 100 ppm in mouse 18-month dietary carcinogenicity study but no details are provided.

Finally, mortality has also been observed in rat studies, although at higher doses. The repetition of observations in various species support the relevance of this effect to human. Moreover, silthiofam has been shown to inhibit the exportation of ATP from the mitochondrial matrix to the cytosol in fungi, leading therefore to cell death due to the disruption of energy-dependant processes (Joseph-Horne et al, 2000). The in vitro testing in rat and human hepatocyte available in the CLH report showed that after sufficient exposure to silthiofam, intracellular ATP production decreases. These observations suggest that this mode of action might be relevant to rat and human, and might explain the observed mortality at high doses. BE CA would appreciate further elaboration regarding a potential mode of action of silthiofam to mammals.

References :
Joseph-Horne T, Heppner C, Headrick J, Hollomon DW - Identification and Characterization of the Mode of Action of MON 65500: A Novel Inhibitor of ATP Export from Mitochondria of the Wheat "Take-All" Fungus, Gaeumannomyces graminis var. tritici. Pesticide Biochemistry and Physiology Volume 67, Issue 3, July 2000, Pages 168-186

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silthiofam.docx

Dossier Submitter's Response

Rabbit data: The RMS assumes that the MS has mixed up the study numbers in their comment. The comment with regard to WI-96-105 does not reflect the text of the CLH report (4.11.2.3 p. 105) and isn't relevant to study WI-95-239 either.

Study WI-96-105 is the main rabbit developmental toxicity study where dose levels were 0, 5, 20 and 60 mg/kg bw/day. There were no mortalities in this study.

Study WI-95-239: The range-finding study: In this study 4/6 dams died between days 13-16 at 100 mg/kg bw day and 5/6 dams died between days 15-22. All relevant data concerning no. of animals, time of death, body weight, clinical signs etc were described.

However, the point being made by the MS comment is that mortality should also be considered as relevant to the STOT RE classification for silthiofam based on the occurrence of mortalities in the dog and the rabbit at dose levels within the cutoff criteria for STOT RE 2. The DS agrees that mortality could be included in the STOT RE proposal.

RAC's response

Although the liver was identified as a target organ in rats, mice and dogs, no classification for STOT RE is considered relevant. Indeed, liver findings observed in rats and mice were

above STOT RE guidance values for classification. Liver toxicity observed in dogs at relevant dose levels did not correlate with histopathological findings and did not progress in severity with longer study duration (28-day, 90-day *vs.* 1-year study).

With regard to lethality, RAC agrees with the DS that classification is warranted based on the rabbit range-finding developmental toxicity study. Mortality observed in dogs supported the classification and suggested that this effect is not rabbit-specific.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Denmark		MemberState	23

Comment received

In a range-finding study in rabbits (WI-95-239), doses of 0, 5, 15, 50, 100 and 150 mg/kg bw/day were given to pregnant rabbits from gestation days 7 through 19.
According to the RAR, four of six and 5/6 females died in the 100 and 150 mg/kg/day dose groups, respectively. Deaths occurred between days 13-16 and 15-22 for gravid females in these respective groups. All deaths except for one intubation error in the 100 mg/kg group were considered treatment-related. A steep dose response was seen in dam mortality as no animals died before caesarian section in the main study (WI-96-105), in which the highest dose given was 60 mg/kg bw/day.
According to the CLP regulation, death is relevant for classification with STOT RE. In the CLH report, classification with STOT RE 2 is proposed based on the observed dam mortality in the rabbit range-finding study.
It may be considered, however, to classify with STOT RE 1 based on the results from the rabbit range-finding study due to the short exposure time to induce death. Death was already observed after 7 days of treatment in the 100 mg/kg bw/day. The guidance values for classification should be adjusted for exposure time according to the CLP regulation:
'The guidance values refer to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure.'
If the actual time of the death observed in the preliminary rabbit developmental study are considered, which are within 7-10 days and 9-13 days of treatment with 100 mg/kg bw/day and 150 mg/kg bw/day, respectively, the first deaths are observed below the guidance value for STOT RE 1 using Harbers rule for extrapolation from the 90 day rat study with a guidance value of 10 mg/kg bw/day:
90 days/7 days x 10 mg/kg bw/day = 129 mg/kg bw/day
Therefore, death of dams observed within 7-9 days dosed with 100 mg/kg bw/day are below the guidance value for STOT RE 1. Death at day 10 in this 100 mg/kg bw/day dose group is just above the extrapolated guidance value, however, as this value should not be considered as a strict cut-off value and due to the severity of the effect, all deaths in the 100 mg/kg bw/day group may trigger STOT RE 1 classification.
There is no evidence presented that (pregnant) rabbits are more sensitive than (pregnant) humans.

Dossier Submitter's Response

Thank you for your comment.
We agree that mortality could be included in the STOT RE proposal.
The guidance document for the CLP Regulation describes a pragmatic approach for dealing with relevant findings in studies of shorter length – "for studies with exposure

durations shorter than 9 days (i.e., 10% of the 90 days to which the default general guidance value applied) the guidance value used should be no greater than 10 times the default values. Therefore, for studies of 9 days (or relevant findings at 9 days) or less should be compared to a guidance value of 1000 mg/kg bw/day for STOT-RE Cat 2 and 100 mg/kg bw/day for Cat 1. At 100 mg/kg bw/day, there was three treatment-related deaths in the rabbit range finding study (WI-95-239), one animal died immediately following dosing of an intubation error. Death occurred at GD 13 (day 6 of dosing), GD 16 (day 9 of dosing) and GD 17 (day 10 of dosing). The DS agrees that all 3 deaths on days 7, 9 and 10 should be considered relevant. The criteria for classification on the basis of mortality have been reached for this study and classification as STOT RE Cat 1 could be considered.
RAC's response
Thank you for your comment and response. RAC agrees with the MS that in this case the actual time of death needs to be considered. Nevertheless, although mortality observed at 100 mg/kg bw/day would be borderline for category 1, effects observed at 150 mg/kg bw/day were within the guidance values for category 2. Therefore, classification for STOT RE in category 2 is considered more appropriate than category 1.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2018	Netherlands		MemberState	24
Comment received				
The NL CA agrees with the proposal to classify Silthiofam as Aquatic Chronic 2 (H411) 'Toxic to aquatic organisms with long lasting effects'.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted by RAC.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2018	United Kingdom		MemberState	25
Comment received				
Silthiofam (ISO) (EC: not available; CAS 175217-20-6) We agree with the Dossier Submitter on their proposal that silthiofam does not require an Aquatic Acute 1 classification as all reliable acute L/EC50 endpoints are > 1 mg/L. We also agree with the proposal for silthiofam to have an Aquatic Chronic 2 classification, as reliable fish and invertebrate chronic NOECs are > 0.1 but ≤ 1 mg/L for an 'not rapidly degradable' substance having a low bioaccumulation potential (according to CLP criteria). We would just like to point out a couple of minor corrections: The lowest acute endpoint is quoted in the overall conclusion Section 5.5 as being the algal 72h EbC50 (biomass) of 8.6 mg/L, whereas for classification purposes it is preferable to use the 72 h ErC50 (growth rate) of 13 mg/L. Since both are > 1 mg/L, this does not affect the acute classification proposal. Also the Aquatic Chronic 2, H411 hazard statement is: 'Toxic to aquatic life with long lasting effects', rather than 'organisms' as proposed in Sections 2.2, 5.5 and 5.6.				

Dossier Submitter's Response
Noted and thank you for your comments.
RAC's response
Noted by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	Netherlands	<confidential>	Company-Manufacturer	26
Comment received				
Certis Europe BV proposed some comments related to the hazardous to the aquatic environment for the following paragraphs in the CLH report: • Paragraphs 1.2 and 1.3 (pages 7 table 2, page 9 table 3 and page 10) Hazardous to the aquatic environment : no classification and no labelling . Reason: The EC10 value is more appropriate than the NOEC for long-term environmental classification with regard to data on long-term aquatic toxicity to fish. The lowest EC10 value determined in the early life-stage toxicity test with the Fathead Minnow (Pimephales promelas) of 1.12 mg/L (mean measured) and the observed NOEC for reproduction of Daphnia magna of 1.8 mg/L (mean measured) are both above the trigger value of 1 mg/L for classification of long-term environmental hazard. Thus, based on the outcome of those long-term aquatic toxicity studies Silthiofam does not need to be classified as long-term aquatic toxic in accordance with CLP Regulation 1272/2008. • Paragraph 5.5 (page 163) Hazardous to the aquatic environment : no classification and no labelling . Reason: The EC10 value is more appropriate than the NOEC for long-term environmental classification with regard to data on long-term aquatic toxicity to fish. The lowest EC10 value determined in the early life-stage toxicity test with the Fathead Minnow (Pimephales promelas) of 1.12 mg/L (mean measured) and the observed NOEC for reproduction of Daphnia magna of 1.8 mg/L (mean measured) are both above the trigger value of 1 mg/L for classification of long-term environmental hazard. Thus, based on the outcome of those long-term aquatic toxicity studies Silthiofam does not need to be classified as long-term aquatic toxic in accordance with CLP Regulation 1272/2008. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180622 Certis comments to CHL silthiofam aquatic environment.zip				
Dossier Submitter's Response				
Noted and thank you for your comments.				
RAC's response				
RAC agrees that for long-term environmental classification in general the EC_{10} value is more appropriate than the NOEC. The reason for this is that the EC_{10} values, as regression-based estimates, are less influenced by dose selection and make full use of the dose response curve. In general the value of the EC_{10} is smaller than the value of the NOEC and leads to a more stringent classification. In the case of the early life-stage toxicity test with the Fathead Minnow (Pimephales promelas) the EC_{10} value is larger than the NOEC which can be explained by the chosen test concentration intervals and by concentration-response modelling. RAC has recalculated the EC_{10} value using the Software ToxRat Professional Version 3.2.1 and found an EC_{10} of 1.059 mg/L with confidence limits of 0.692 and 1.621 indicating the uncertainty of the EC_{10} value close to the border of classification criteria. RAC notes, that the OECD TG 211 states that growth measurements are highly desirable since they provide information on possible sub-lethal effects, which may be useful in				

addition to reproduction measures alone; the measurement of the length of the parent animals (i.e. body length excluding the anal spine) at the end of the test is recommended. The reporting may include any appropriate justification. Moreover, following the same Guideline, a justification is not obligatory, which means that a missing justification does not invalidate the result as such. The endpoint growth based on length per se is undoubtful a relevant endpoint for the purpose of classification.

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2018	France		MemberState	27
Comment received				
FR agrees with the classification proposed for Environmental hazards.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted by RAC.				

PUBLIC ATTACHMENTS
1. Silthiofam.docx [Please refer to comment No. 2, 9, 14, 22]

CONFIDENTIAL ATTACHMENTS
1. 20180622 file 6 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip [Please refer to comment No. 3, 16]
2. 20180622 file 5 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip [Please refer to comment No. 4, 17]
3. 20180622 file 4 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip [Please refer to comment No. 5, 18]
4. 20180622 file 3 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip [Please refer to comment No. 6, 19]
5. 20180622 file 2 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip [Please refer to comment No. 7, 20]
6. 20180622 file 1 of 6 Certis comments to CHL silthiofam reproductive toxicity.zip [Please refer to comment No. 8, 21]
7. 20180622 Certis comments to CHL silthiofam aquatic environment.zip [Please refer to comment No. 26]

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILTHIOFAM (ISO); *N*-ALLYL-4,5-DIMETHYL-2-(TRIMETHYLSILYL)THIOPHENE-3-CARBOXAMIDE

Appendix 1: Response to Comment 14 (Belgium)

Summary of malformations found in WIL-50244 (Study Table 14, p 56)

	Foetuses				Litters			
Dose (mg/kg bw/day)	**0**	**5**	**20**	**60**	**0**	**5**	**20**	**60**
No. examined externally	**57**	**89**	**86**	**73**	**11**	**17**	**14**	**17**
Short tail	1	0	0	0	1	0	0	0
Gastroshcisis	0	0	0	##1	0	0	0	1
Mandibular agnathia	*1	0	0	0	1	0	0	0
Maxillary agnathia	*1	0	0	0	1	0	0	0
Proboscis-like nose	*1	0	0	0	1	0	0	0
Astomia	*1	0	0	0	1	0	0	0
Aglossia	*1	0	0	0	1	0	0	0
Micropthalmia and/or Anophthalmia	*1	0	0	0	1	0	0	0
Microcephaly	*1	0	0	0	1	0	0	0
Pinna(e) malpositioned	*1	0	0	0	1	0	0	0
Omphalocele	0	1	0	0	0	1	0	0
No. examined viscerally	**57**	**89**	**86**	**73**	**11**	**17**	**14**	**13**
Hydrocephaly	*1	0	0	1	1	0	0	1
Spleen absent	#1	0	0	0	1	0	0	0
Heart and/or great vessel anomaly	#1	0	0	0	1	0	0	0
Malpositioned kidney(s)	0	0	1	0	0	0	1	0
Fused ureters	0	0	1	0	0	0	1	0
Retro-oesophageal aortic arch	0	0	1	0	0	0	1	0
Tracheal anomaly	0	0	1	0	0	0	1	0
Number examined skeletally	**57**	**89**	**86**	**73**	**11**	**17**	**14**	**13**
Vertebral anomaly with or without associated rib anomaly	2	1	3	1	2	1	3	1
Sternoschisis								
Skull anomaly	0	0	0	##1	0	0	0	1
	0	0	1	0	0	0	1	0

*Single foetus (no. 6) from litter 20758
#single foetus (no 9) from litter 20758
single foetus (no 6) from litter 20739
**No findings significantly different from controls using Fishers Exact test.